

**AWARD NUMBER:** W81XWH-20-1-0871

**TITLE:** **Genome-Wide Association Study in Acquired Aplastic Anemia**

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**CONTRACTING ORGANIZATION:** The Geneva Foundation  
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**REPORT DATE:** September 2022

**TYPE OF REPORT:** Annual

**PREPARED FOR:** U.S. Army Medical Research and Development Command  
Fort Detrick, Maryland 21702-5012

**DISTRIBUTION STATEMENT:** Approved for Public Release;  
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# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

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<b>1. REPORT DATE</b> SEPTEMBER 2022		<b>2. REPORT TYPE</b> Annual report		<b>3. DATES COVERED</b> 9/1/2021-8/31/2022	
<b>4. TITLE AND SUBTITLE</b>  Genome-Wide Association Study in Acquired Aplastic Anemia				<b>5a. CONTRACT NUMBER</b> W81XWH-20-1-0871	
				<b>5b. GRANT NUMBER</b>	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Dr. Neal Young Youngns@nhlbi.nih.gov				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  The Geneva Foundation 917 Pacific Avenue. Suite 600 Tacoma, WA 98402				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Aplastic Anemia (AA) is a previously universally fatal disease characterized by a hypocellular bone marrow and pancytopenia. AA incidence is skewed across the globe, being 2-3 fold higher in Asia than in Europe. In a variety of studies, chemical exposures and infections in different geographic areas have been described as risk factors for AA, but inconsistently, based on small sample sizes, and at prevalence too low to account for large geographic differences. Genome wide association study GWAS is a powerful research method that compiles genetic variants from many individuals to investigate the association of common genetic markers with a disease phenotype. It has led to the discovery of important new genes and associations in a number of medical conditions.					
<b>15. SUBJECT TERMS</b> Aplastic Anemia, Hematology					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  Unclassified	<b>18. NUMBER OF PAGES</b>  15	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRDC
<b>a. REPORT</b>  Unclassified	<b>b. ABSTRACT</b>  Unclassified	<b>c. THIS PAGE</b>  Unclassified			<b>19b. TELEPHONE NUMBER</b> (include area code)

Standard Form 298 (Rev. 8-98)  
Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

DNA samples of AA patients from United States/Europe (n=840) and Asia (n=900) will be genotyped on the GSA v3 Illumina chip in the National Institutes of Health, USA. The new data scan will undergo meta-analysis with existing data from American (n=802), UK (n=665), and Korean populations (n=131) to identify major differences in allele frequencies by ancestry. Experimental follow up will be performed on potentially identified loci in order to investigate novel biological mechanisms. This is a pioneering international multi-ethnic GWAS study that aims to investigate still unexplained higher AA incidence in those of Asian ancestry. As the largest and most ethnically diverse GWAS in AA we aim to have sufficient power to reveal new traits that account for the heterogeneity and give insight into the genomic landscape of AA. Immune AA is a complex disease in which the pathophysiology is still not completely understood. By unraveling the genetics of AA through the unbiased approach of GWAS, we expect to identify novel mechanisms that underlie AA and potentially reveal new targets for therapies.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Aplastic Anemia, Hematology

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

**What were the major goals of the project?**

*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

Specific Aim 1: Genome Wide Association Study in Aplastic Anemia

Specific Aim 2: Discovery of novel common variants associated with increased AA risk and etiology in different populations.

Specific Aim 3: Meta-analysis to increase statistical power to detect common variants

Specific Aim 4: Post-GWAS experiments to validate identified risk loci with translational potential

**What was accomplished under these goals?**

*For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

**Aim 1:**

Further progress has been made for the acquisition of samples which have now arrived from Kanazawa University in Japan and Nagoya University in Japan. These are currently in our laboratory awaiting transfer to the NCI for GWAS to be performed (all samples must be processed for GWAS simultaneously so we must wait for all samples to arrive). Delays have been encountered in samples from Chonnam University in South Korea and our European collaborators. Delays in Chonnam relate to institutional funding required for sample processing (this is currently being sought). Delays with European collaborators are due to IRB restrictions in Europe which collaborators are working on.

We have also identified an additional 6000 Korean Control samples freely available from a collaborator in NCI who will make data available to us and will likely make the South Korean control samples unnecessary.

We hope now to complete aim 1 in early/mid 2023 – this will involve transfer of all de-identified DNA to the National Cancer Institute to be run on the GWAS chip. Aims 2-4 will depend on the successful completion of aim 1. Samples are all required to be sequenced simultaneously so we require resolution of the funding issue with South Korean samples and the IRB issue with European collaborators.

**What opportunities for training and professional development has the project provided?**

*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

Nothing to report

**How were the results disseminated to communities of interest?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of*

*these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

Nothing to report

**What do you plan to do during the next reporting period to accomplish the goals?**

*If this is the final report, state “Nothing to Report.”*

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

Our main goal will be to get the remaining samples shipped samples to allow sequencing.

We are in the process of working on an agreement with South Korean collaborators to allow funding for sample processing. We have also been in constant contact with European collaborators as they are trying to resolve their issues with IRB.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

**What was the impact on the development of the principal discipline(s) of the project?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

Nothing to report

**What was the impact on other disciplines?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

Nothing to report

**What was the impact on technology transfer?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

*Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:*

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report

**Actual or anticipated problems or delays and actions or plans to resolve them**

*Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

We have encountered a significant delay in sample shipment from some collaborators – European collaborators is due to ethical institutional approval which is still ongoing. The issue with Chonnam University in South Korea is due to required funding for sample processing. We have discussed with Geneva and are working with our collaborators currently to come up with a support plan.

**Changes that had a significant impact on expenditures**

*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

We have run into an issue with Chonnam University requiring funding for sample processing. We are working on a funding agreement to provide this – we are waiting to hear back which specific costs they are requesting.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee*

*(or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

**Significant changes in use or care of human subjects**

Nothing to report

**Significant changes in use or care of vertebrate animals**

Nothing to report

**Significant changes in use of biohazards and/or select agents**

Nothing to report

**6. PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

- **Publications, conference papers, and presentations**

*Report only the major publication(s) resulting from the work under this award.*

**Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal;*

*volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

**Books or other non-periodical, one-time publications.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

**Other publications, conference papers and presentations.** *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (\*) if presentation produced a manuscript.*

Nothing to report

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

#### Example:

Name: *Mary Smith*  
Project Role: *Graduate Student*  
Researcher Identifier (e.g. ORCID ID): *1234567*  
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*

Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Neal S. Young  
Project Role: PI  
Contribution to Project: Dr. Young has provided oversight for the project, was involved in the study design and editing of the protocol, and his lab and staff have carried out processing of samples.

Name: Sharon Savage  
Project Role: Collaborator  
Researcher Identifier (e.g. ORCID ID):  
Nearest person month worked: 0.5  
Contribution to Project: Dr. Savage has been coordinating things in regards to the technical aspects of sample preparation for the GWAS as well as organizing local genomics committee within the National Cancer Institute authorization of the project to go ahead.

Name: Emma Groarke  
Project Role: Co-Investigator  
Researcher Identifier (e.g. ORCID ID): 0000-0002-4648-5926  
Nearest person month worked: 6  
Contribution to Project: Dr. Groarke has authored the study protocol, obtained approval from the NIH IRB and HPRO, obtained clinical data for 600 NIH samples, coordinated with NCI regarding study design and sample specifications, acted as a coordinator with all international collaborators to allow for local ethical approval and signing of research agreements, and liaised with Geneva regarding all required documentation.

Name: Fernanda Gutierrez-Rodrigues  
Project Role: Co-Investigator  
Researcher Identifier (e.g. ORCID ID): 0000-0003-3116-4588  
Nearest person month worked: 6  
Contribution to Project: Dr. Gutierrez-Rodrigues has coordinated the processing of samples within the lab including sample selection, sorting, and DNA extraction of all 600 samples .

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

Chonnam National University, South Korea - collaborators will now only be providing AA samples, not controls

## What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- Financial support;
- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner’s facilities for project activities);
- Collaboration (e.g., partner’s staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and
- Other.

Kanazawa University, Japan – collaborators who are providing samples Chonnam National University, South Korea - collaborators who are providing samples King’s College London, UK - collaborators who are providing samples Hospital Saint-Louis, France - collaborators who are providing samples Universita Degli Studi Di Napoli Federico II, Italy - collaborators who are providing samples RIKEN, Japan - collaborators who are providing control data National Institute of Haematology – Blood Transfusion, Vietnam - collaborators who are providing samples Nagoya University, Japan - collaborators who are providing samples St. James’s Hospital, Dublin, Ireland - collaborators who are providing samples
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## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:** For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org/eBRAP/public/index.htm> for each unique award.

**QUAD CHARTS:** If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.